FORCE Platform for Delivery of Oligonucleotides for the Treatment of DM1 and DMD: Moving from Bench to Clinic with DYNE-101 and DYNE-251

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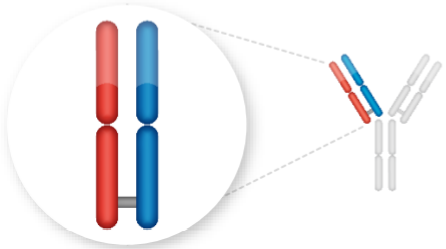
Dyne's FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

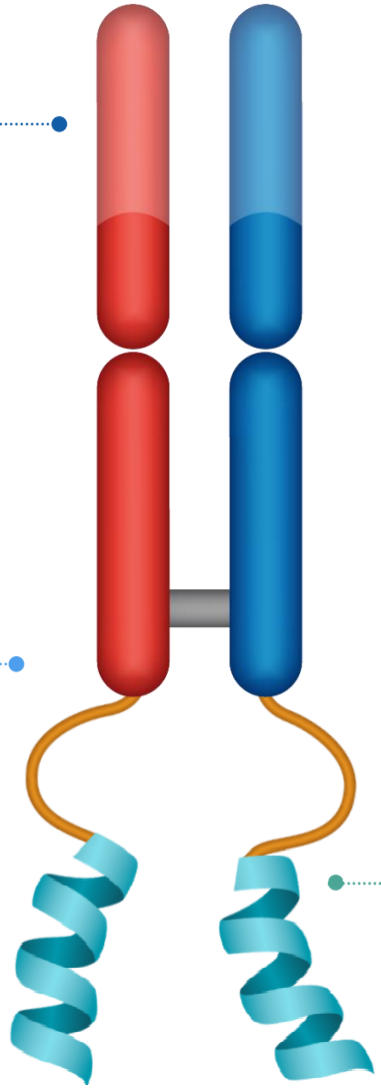
ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



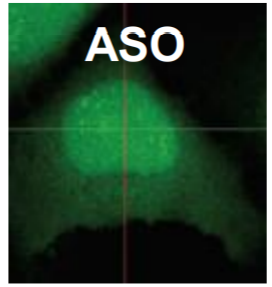
LINKER

Clinically validated, enables precise conjugation of multiple payloads to a single Fab



PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease

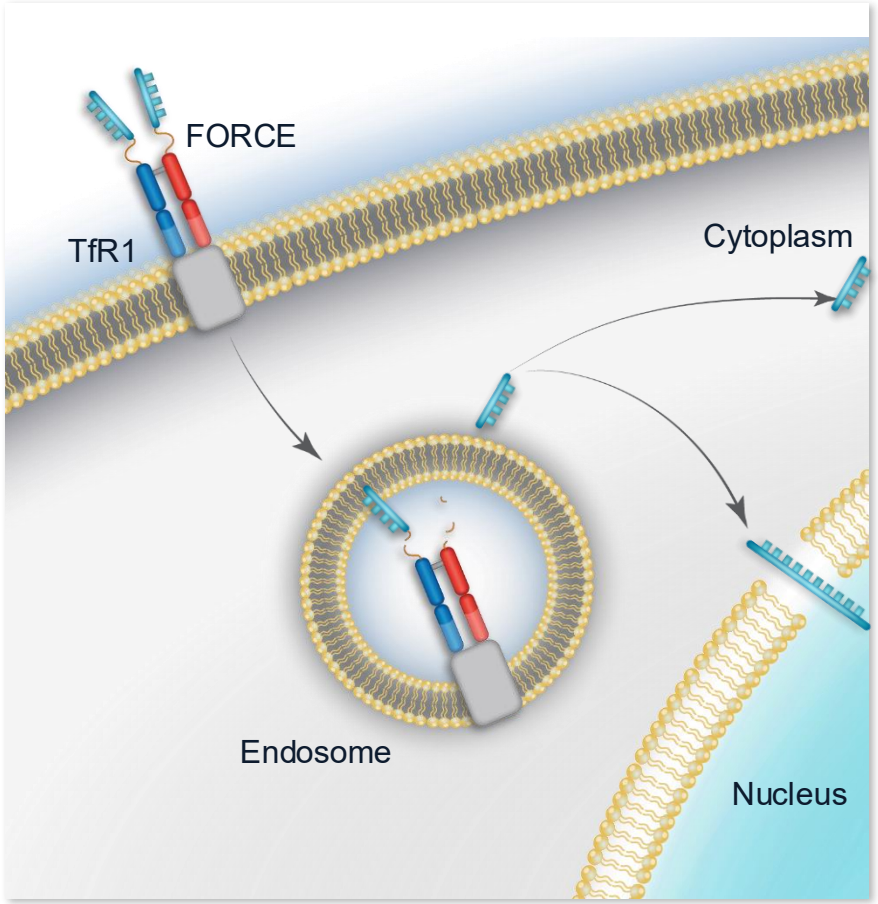


Nuclear localization

Cytoplasmic localization

Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369

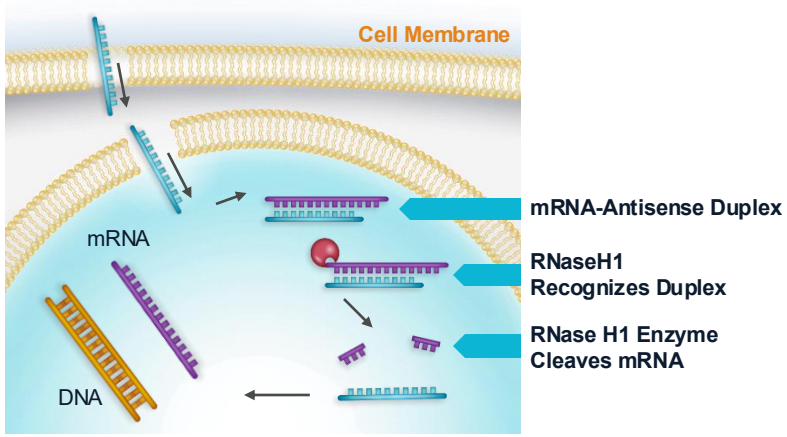
FORCE Platform Harnesses Cell Biology to Modify Disease



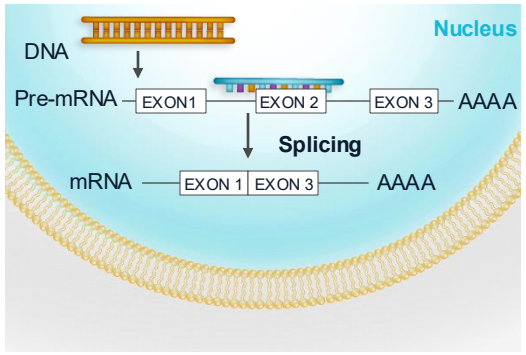
- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

Rationally Select Payload to Target Genetic Basis of Disease

ASO acts in the nucleus and cytoplasm

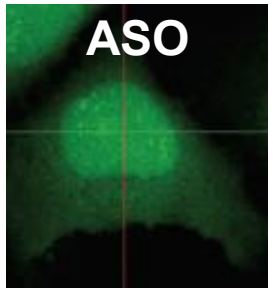


Splice-modulating ASO



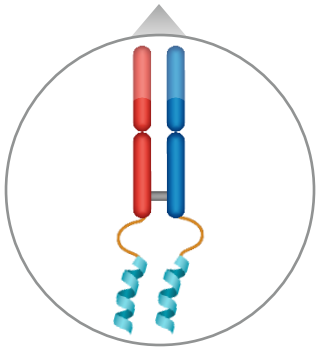
Single-Stranded Antisense

Subcellular distribution of ASO and siRNA



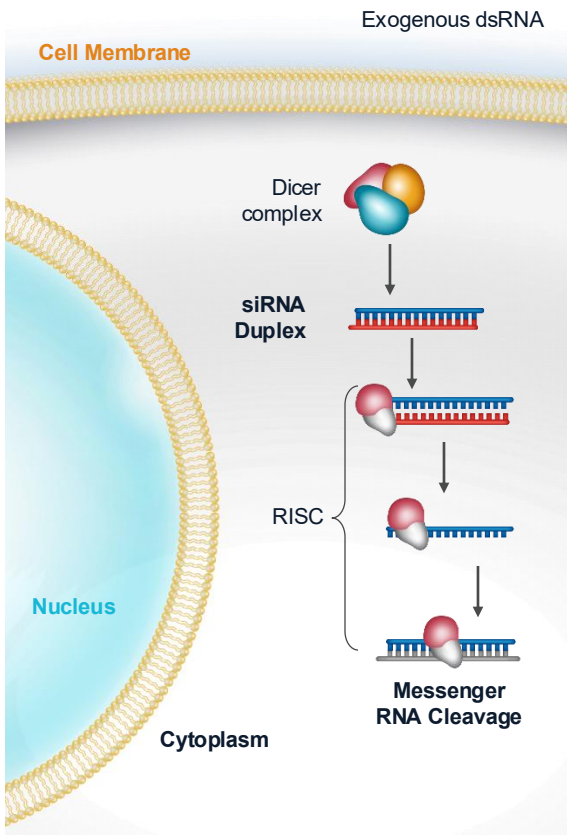
Nuclear localization

Cytoplasmic localization



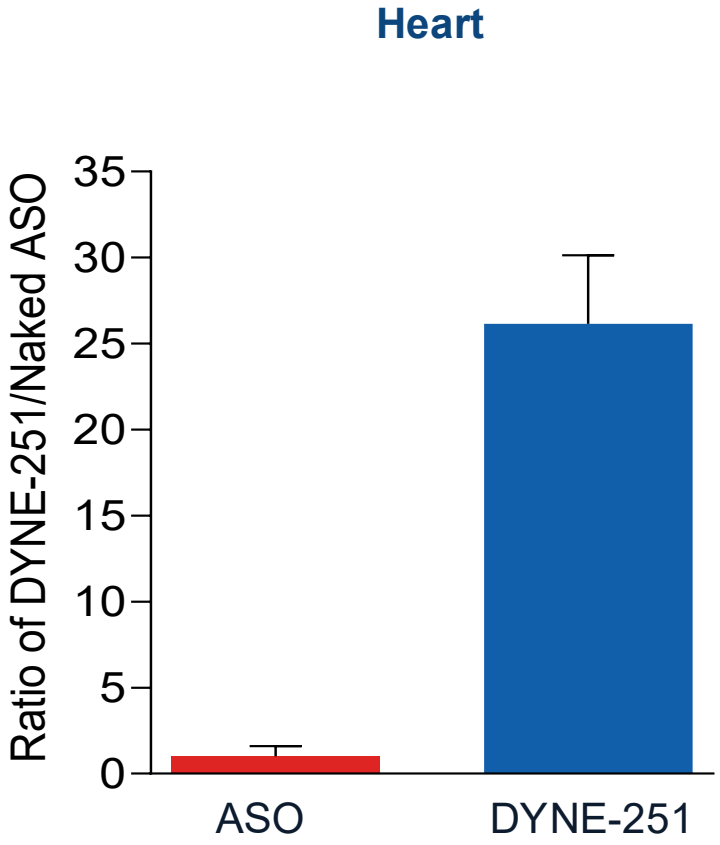
FORCE delivers **ASO** payload for nuclear targets, **siRNA** payload for cytoplasmic targets

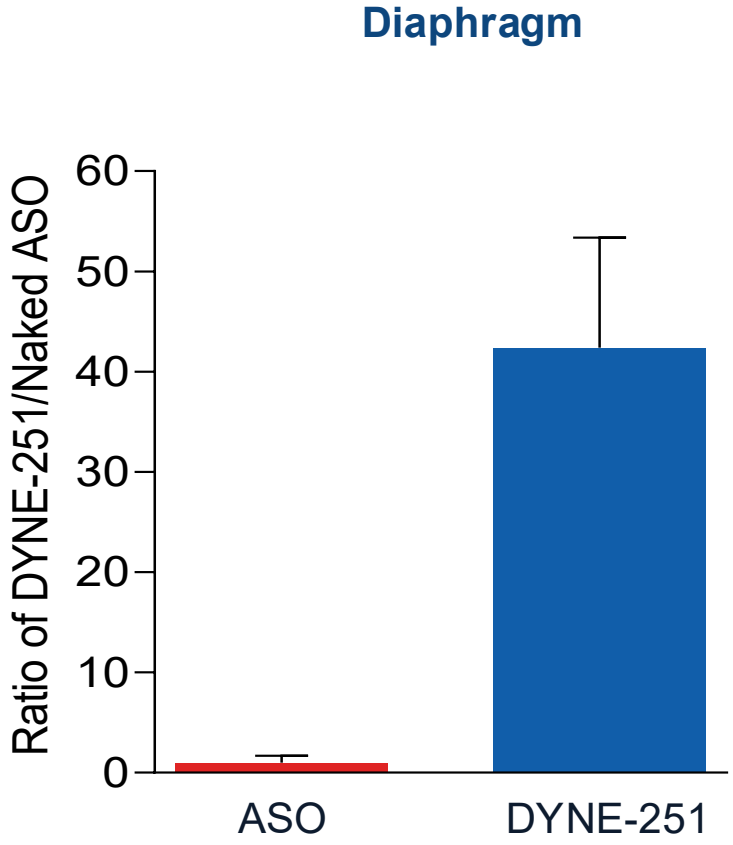
siRNA acts in the cytoplasm



Double-Stranded Antisense (siRNA)

FORCE's Targeted Delivery Brings the Power of Modern Oligo Therapeutics to Patients Living with Serious Muscle Diseases





Note: Results after repeat IV dose of naked ASO or DYNE-251 in male cynomolgus monkeys, 2 x 30 mg/kg on day 0 and day 7, analyzed day 28; n = 4 – 5

Developing Transformative Therapies for People Living with DM1

Overview

- Mutation in the *DMPK* gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

Population

- >40,000 (US)
- >74,000 (Europe)

NO approved therapies

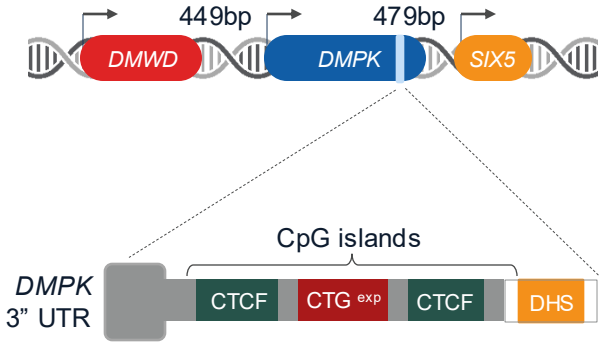
OUR APPROACH

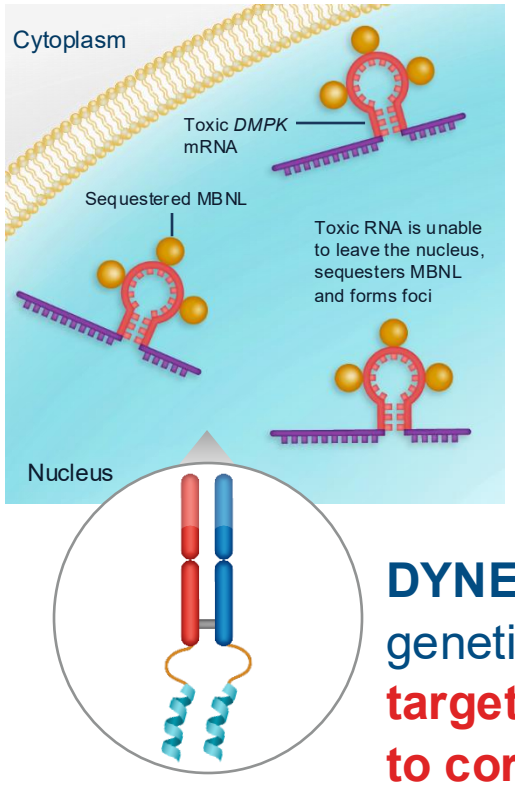
Disease-Modifying Nuclear *DMPK* Knockdown

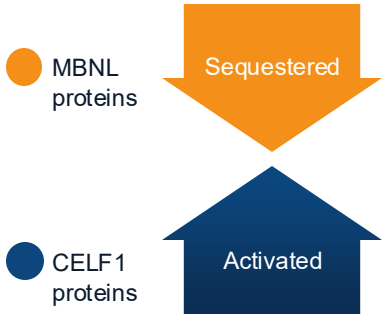
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE targets the genetic basis of DM1 to correct splicing

DNA Triplet Repeats → **Toxic RNA Forms Foci in Nucleus** → **RNA Binds Splicing Proteins** → **Clinical Presentation**



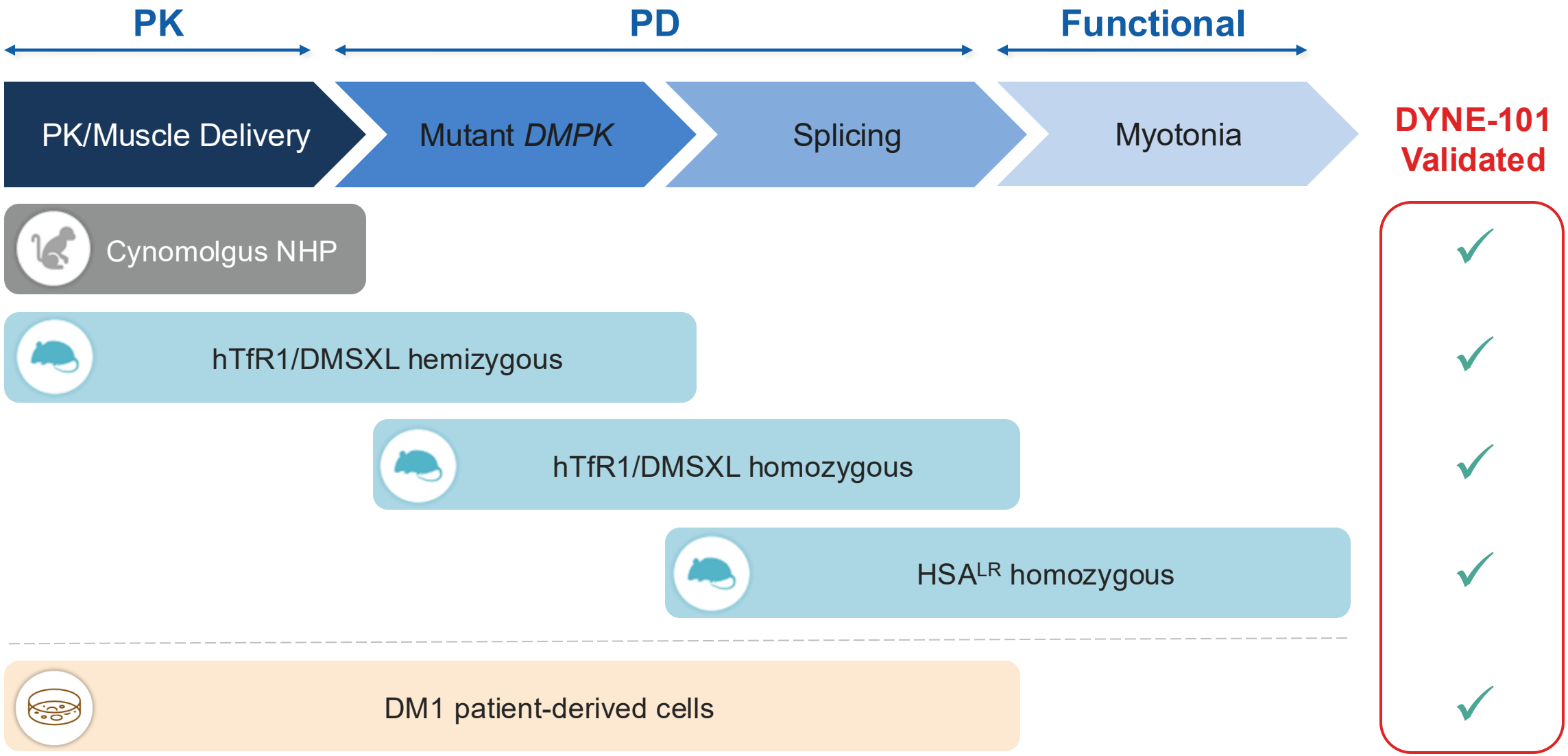




- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

DYNE-101 designed to address the genetic basis of disease by **targeting toxic nuclear *DMPK* RNA to correct spliceopathy**

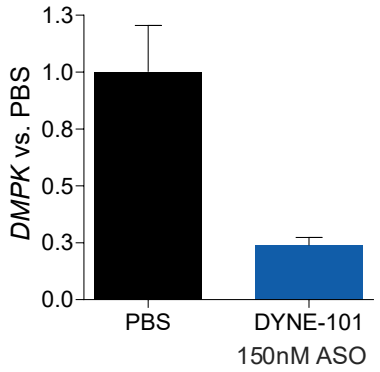
Robust Preclinical Data Supporting the Potential of DYNE-101 to Drive Disease Modification in the Clinic



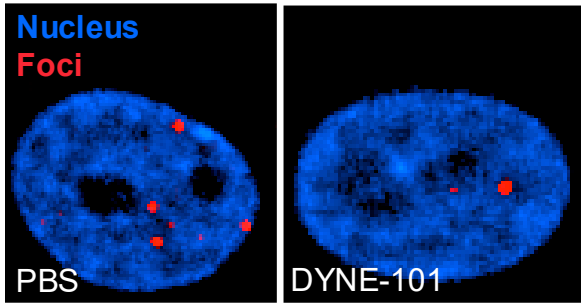
DYNE-101 Demonstrated Robust Dose-dependent *DMPK* KD, Foci Reduction, and Splicing Correction

380 CTG Repeats DM1 Myotubes

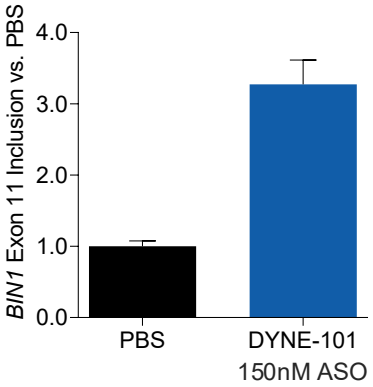
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

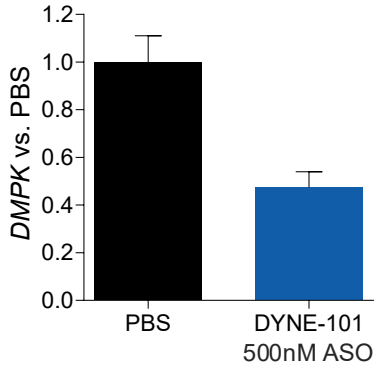


BIN1 mis-splicing correction by qPCR

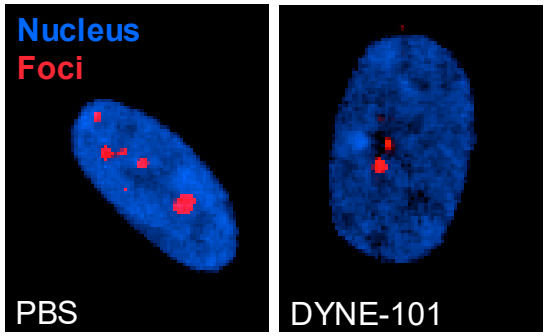


2,600 CTG Repeats DM1 Myotubes

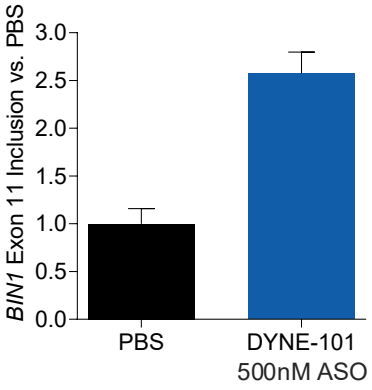
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

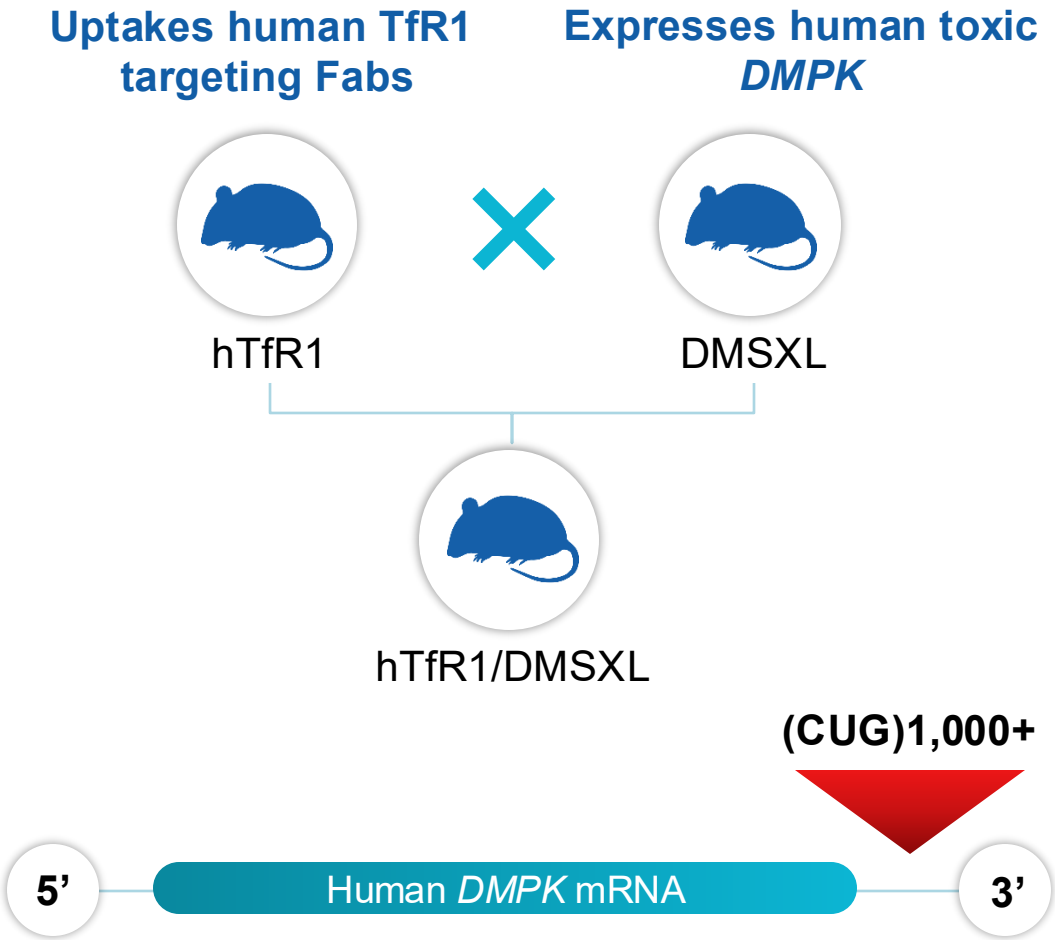


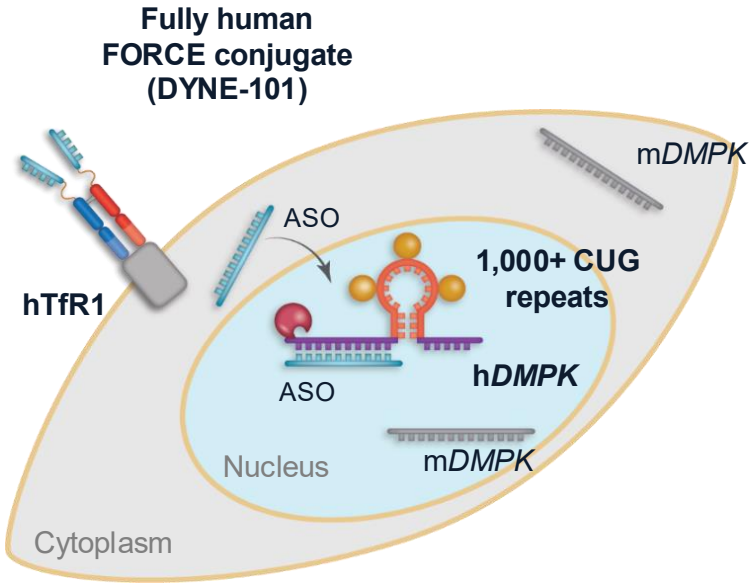
BIN1 mis-splicing correction by qPCR



Note: Data are mean ±SD, n=4. Foci reduction based on foci area corrected for nuclear area

hTfR1/DMSXL: Innovative Model Developed by Dyne to Evaluate PD by Measuring Toxic Human Nuclear *DMPK* KD



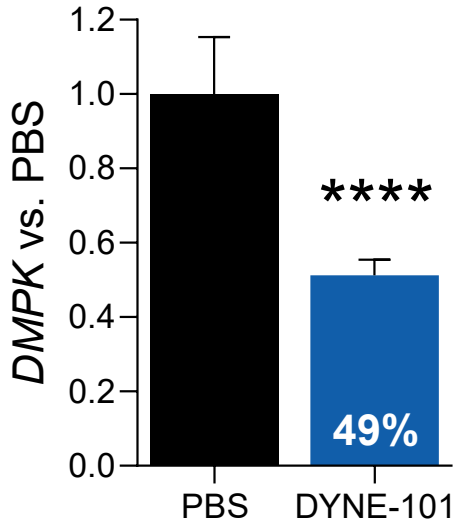


- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fab
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

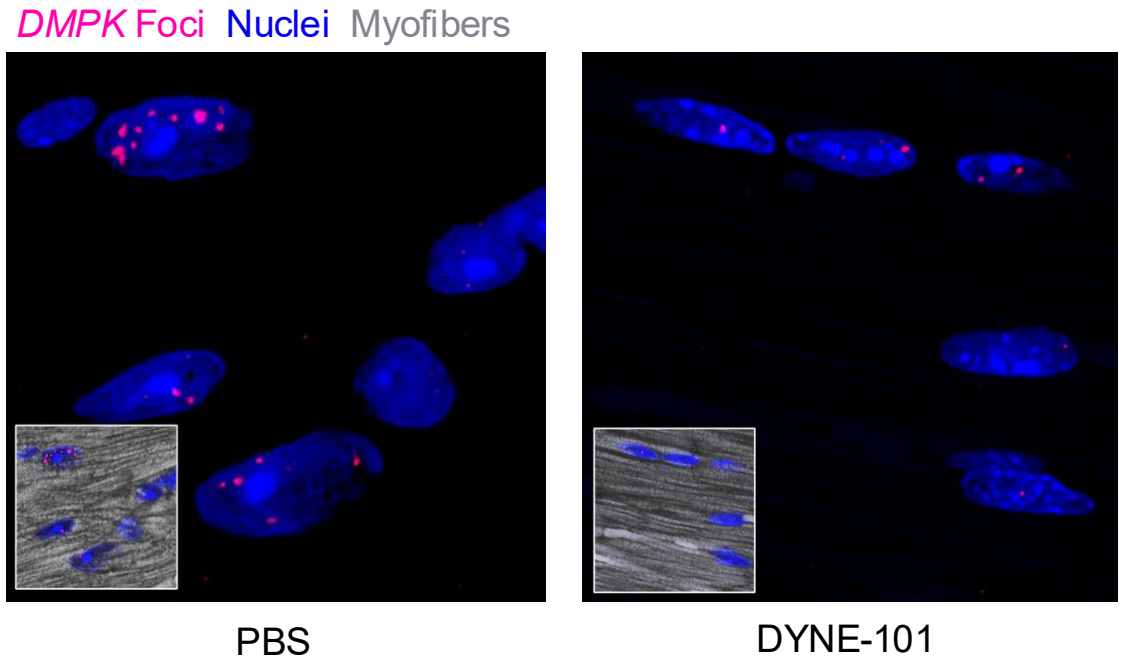
Note: DMSXL mice first described in PLOS Genetics 2012, 8(11):e1003043

DYNE-101 Demonstrated Toxic Human *DMPK* KD, Foci Reduction, and Splicing Correction in Heart of hTfR1/DMSXL Mice

Toxic human *DMPK* expression (%KD)

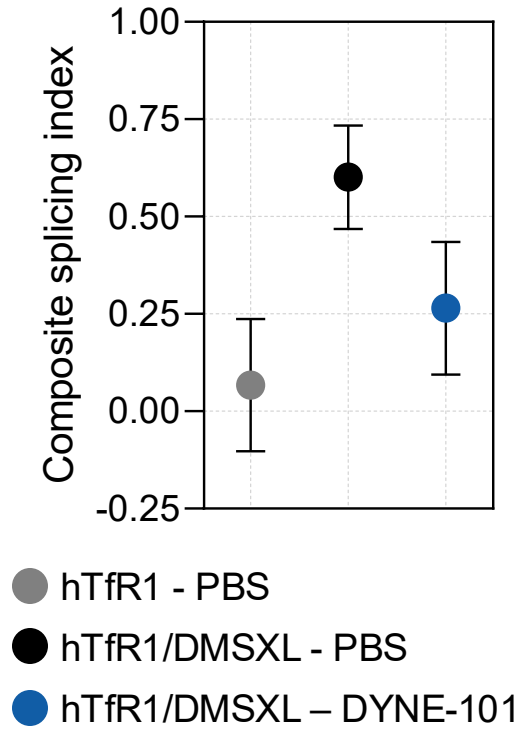


Toxic human *DMPK* foci reduction



DYNE-101 reduces foci area by 49%*

Splicing correction

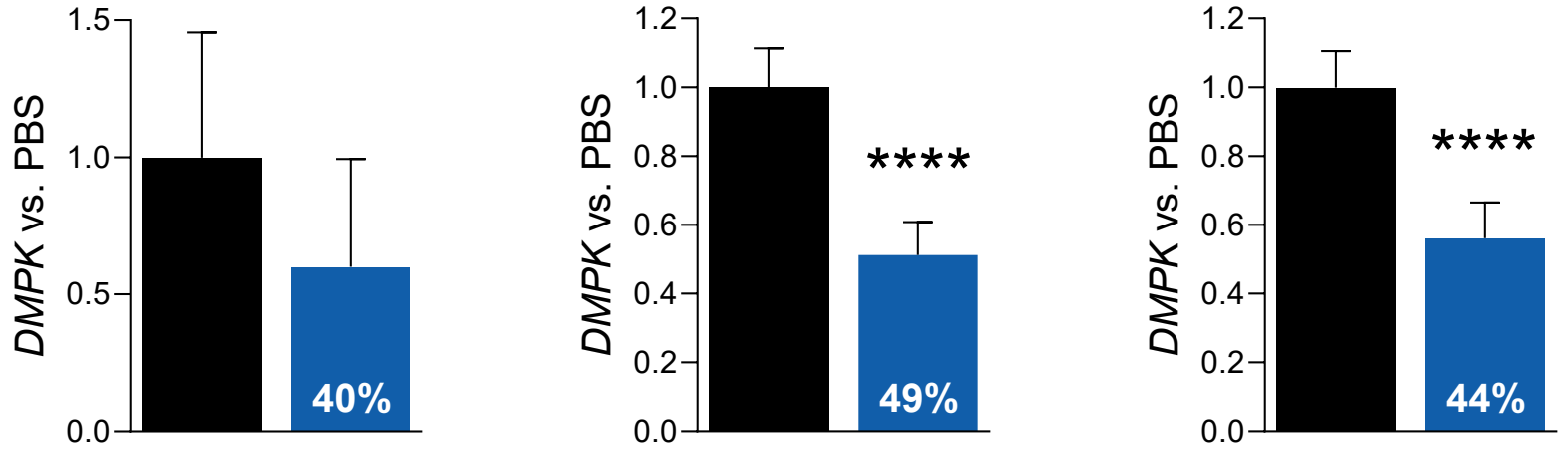


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are means ± SD, n = 6 – 7 per arm; * p <0.05, **** p < 0.0001 significant by *t*-test

DYNE-101 Demonstrated Toxic Human *DMPK* KD and Splicing Correction in Skeletal Muscle of hTfR1/DMSXL Mice

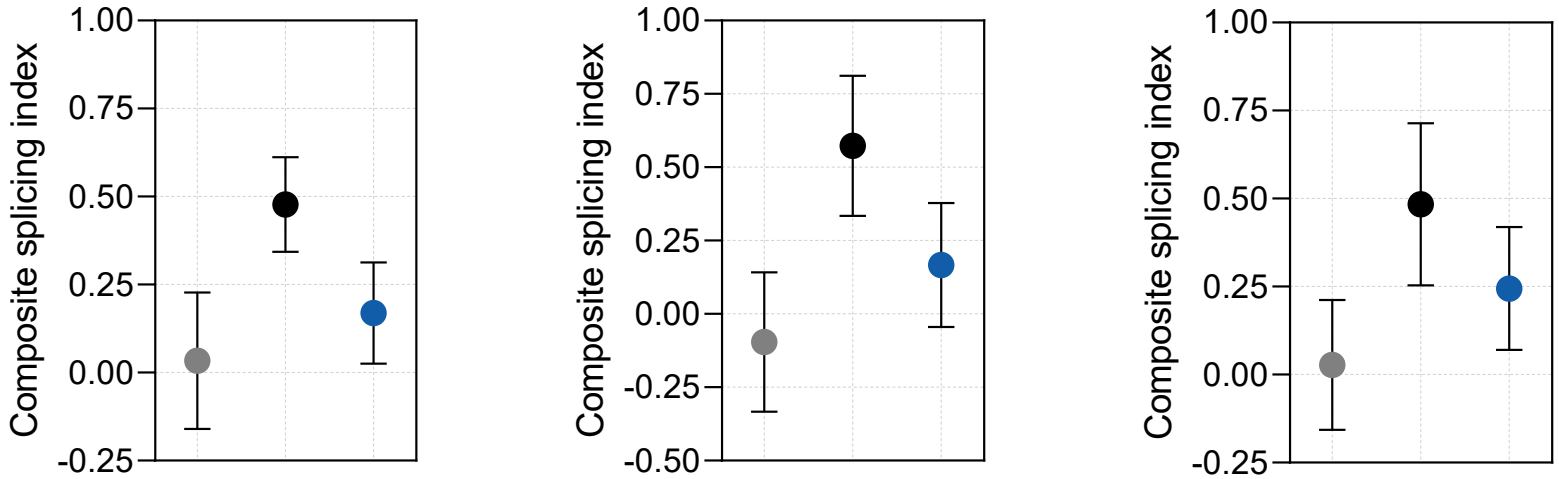
Toxic human *DMPK* expression (% KD)

- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101



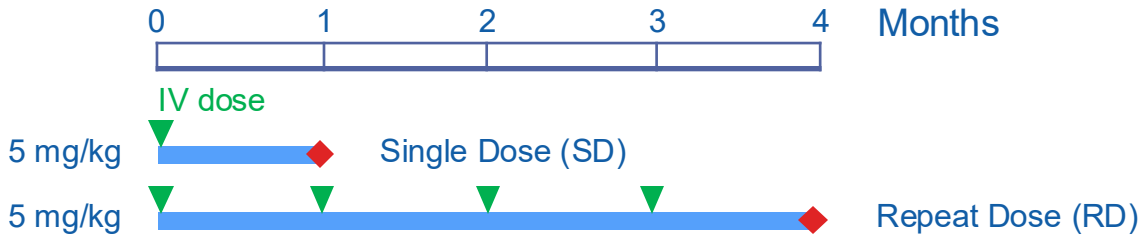
Splicing correction

- hTfR1 - PBS
- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101

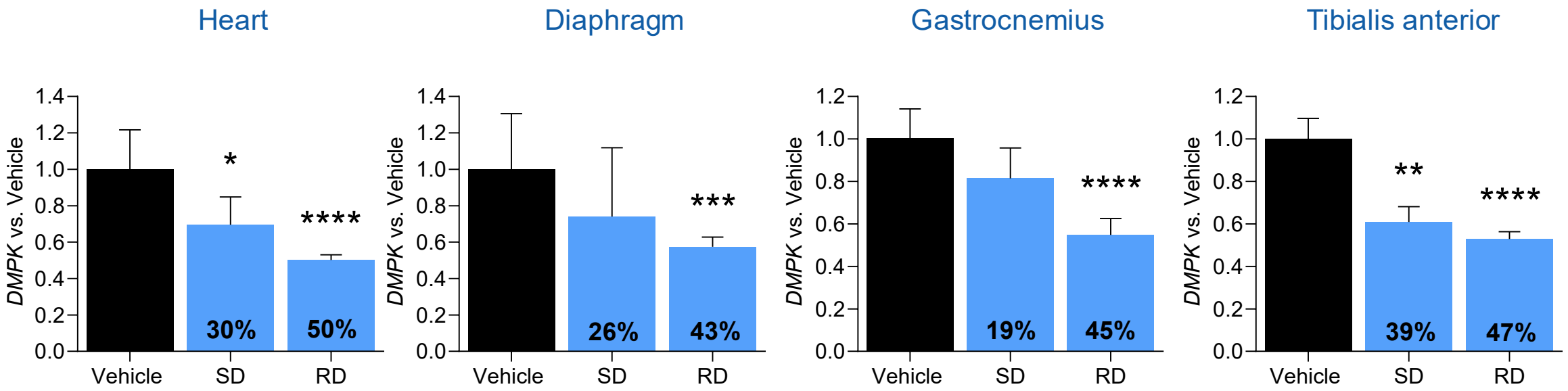


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing indices include *Bin1* E11, *Insr* E11, *Ldb3* E11, *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 mis-splicing measured by qRT-PCR. Data are means ± SD; n = 4 – 7; **** $p < 0.0001$ by *t*-test

Low Monthly Dosing of DYNE-101 in hTfR1/DMSXL Mice Enhanced Toxic Human *DMPK* KD in Cardiac and Skeletal Muscle

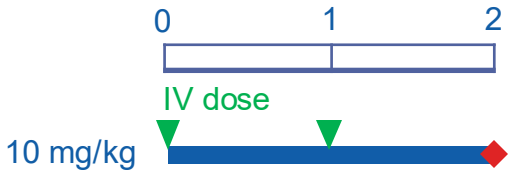


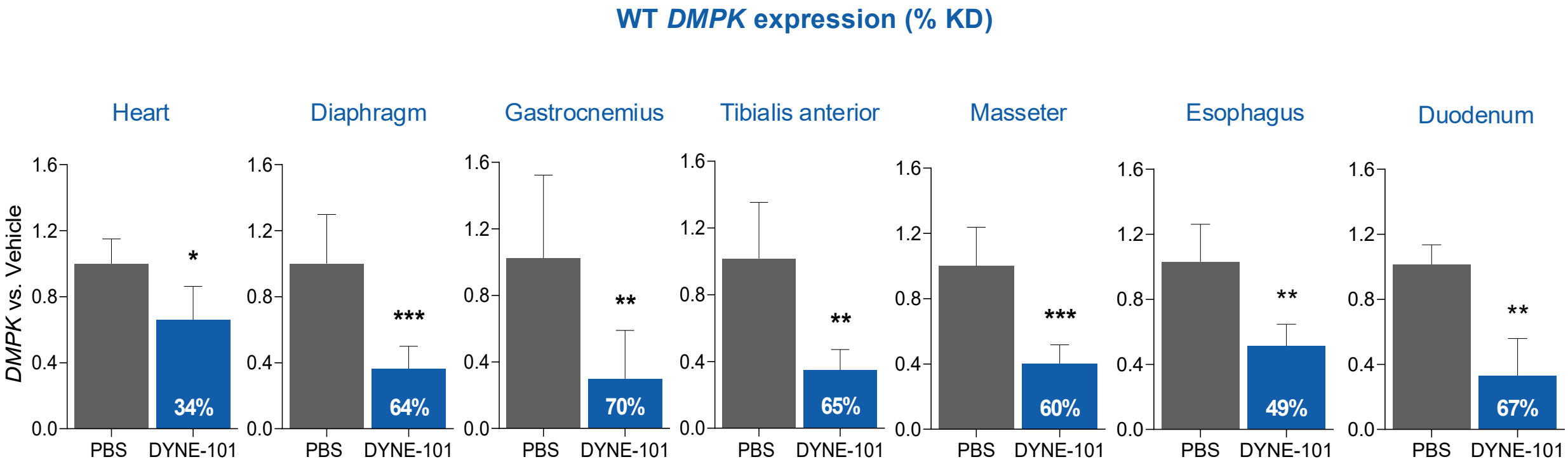
Toxic human *DMPK* expression (% KD)



Note: hTfR1/DMSXL hemizygous mice. Data are means ± SD; n = 4 - 6 per arm; *p< 0.05, **p< 0.01, ***p< 0.001, ****p< 0.0001 significant by One-way ANOVA

Repeat Monthly Dosing of DYNE-101 in NHPs Achieved Significant WT *DMPK* KD Demonstrating Translatability to Higher Species





Note: Male cynomolgus monkeys. Data are means ± SD; n = 3 - 4 per arm; * $p<0.05$, ** $p< 0.01$, *** $p< 0.001$ significant by One-way ANOVA

DYNE-101 Achieved *DMPK* Knockdown & Well Tolerated in NHPs

Robust WT *DMPK* KD Achieved in Skeletal, Cardiac and Smooth Muscles

- Up to 70% *DMPK* KD at 2 months with low monthly dosing

13-Week GLP Toxicology Study[1]

- No dose limiting toxicity observed up to a maximally feasible dose[2]
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested

Notes: 1. Based on conclusions of report from third-party CRO. 2. Dosed once every three weeks
NOAEL: No-observed-adverse-effect level

Phase 1/2 Clinical Trial to Evaluate DYNE-101 in Patients with DM1

Population

- Adult patients living with DM1
- Ages 18 to 49 years
- ~64 adult participants

Primary Endpoints

- Safety and tolerability

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function

Stages of ACHIEVE

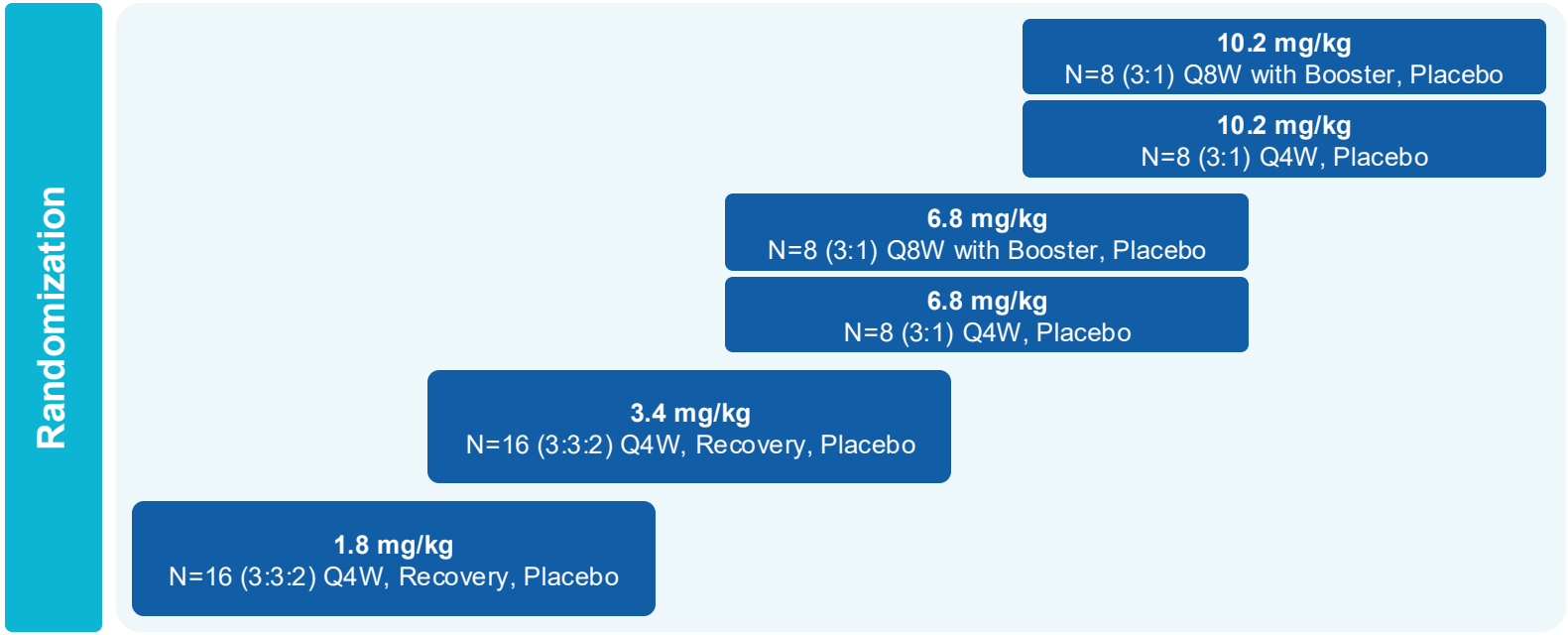
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Splicing Data Expected in H2 2023

Multiple Ascending Dose Stage of ACHIEVE

ACHIEVE

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly or Less Frequent Administration of DYNE-101 in ~64 Adult Patients Living with DM1



MAD Study Details

- IV administration of DYNE-101 or placebo every 4 weeks or every 8 weeks
- Muscle biopsies: Baseline, 12 weeks, 24 weeks
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Strategy & Adaptive Trial Design Enable Rapid Achievement of Potentially Registrational Clinical Data

Doses provided refer to ASO component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing

Building a Global DMD Franchise of Transformative Therapies

Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)

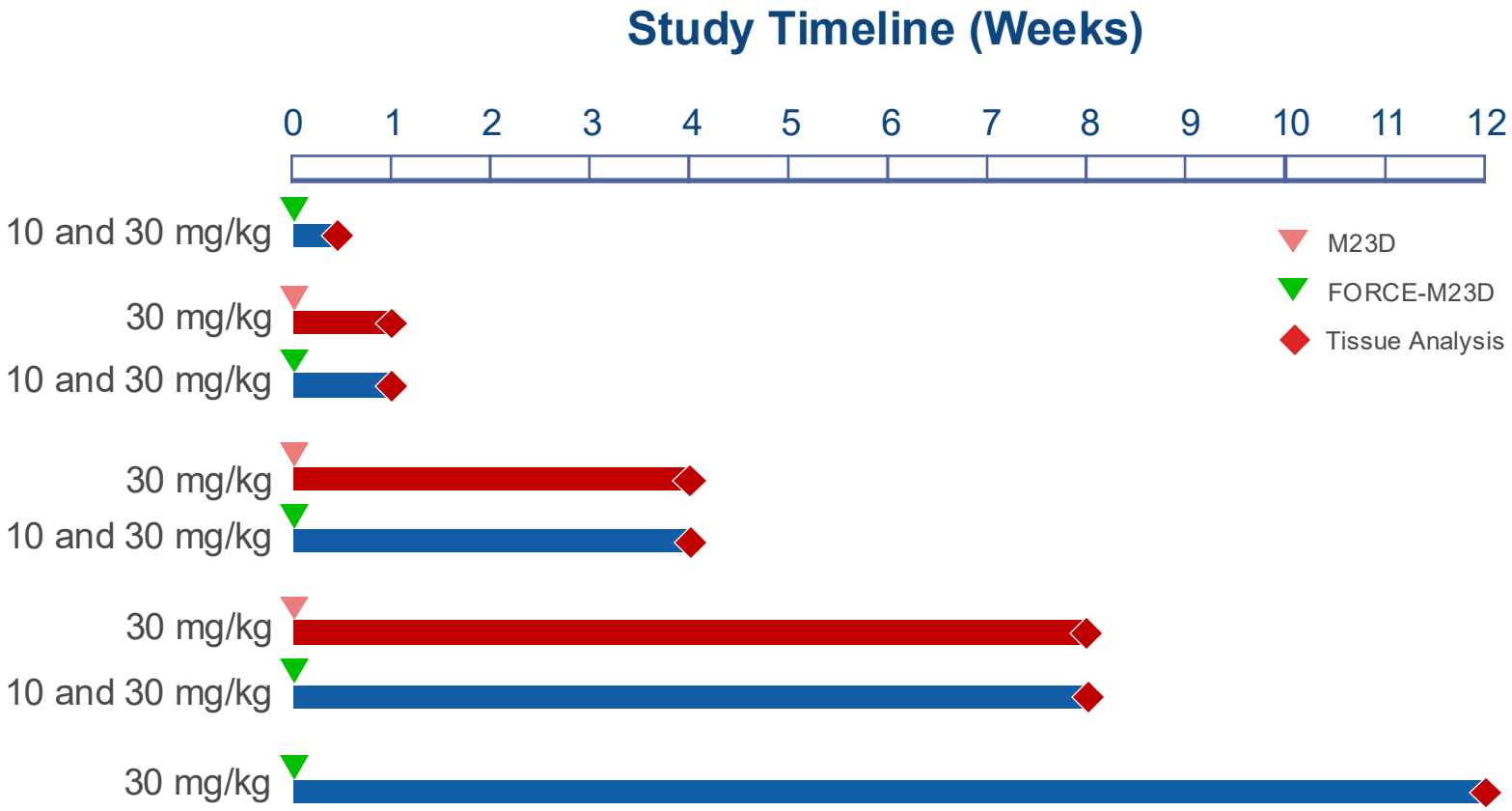
Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

OUR APPROACH

Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

Study Evaluated Dynamic of FORCE-M23D and M23D on Dystrophin Expression up to 12 Weeks After a Single Dose



Endpoints

- ASO muscle concentration
- Exon skipping by PCR
- Dystrophin protein by WB
- Dystrophin localization by IF

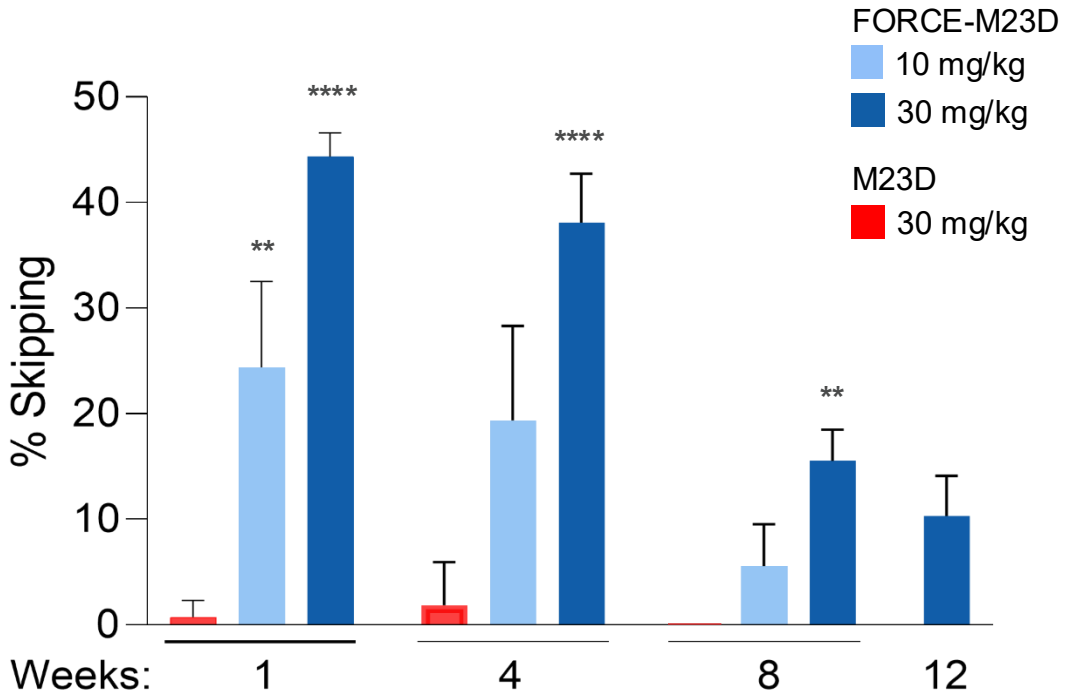
Tissues analyzed

- Quadriceps
- Diaphragm
- Heart

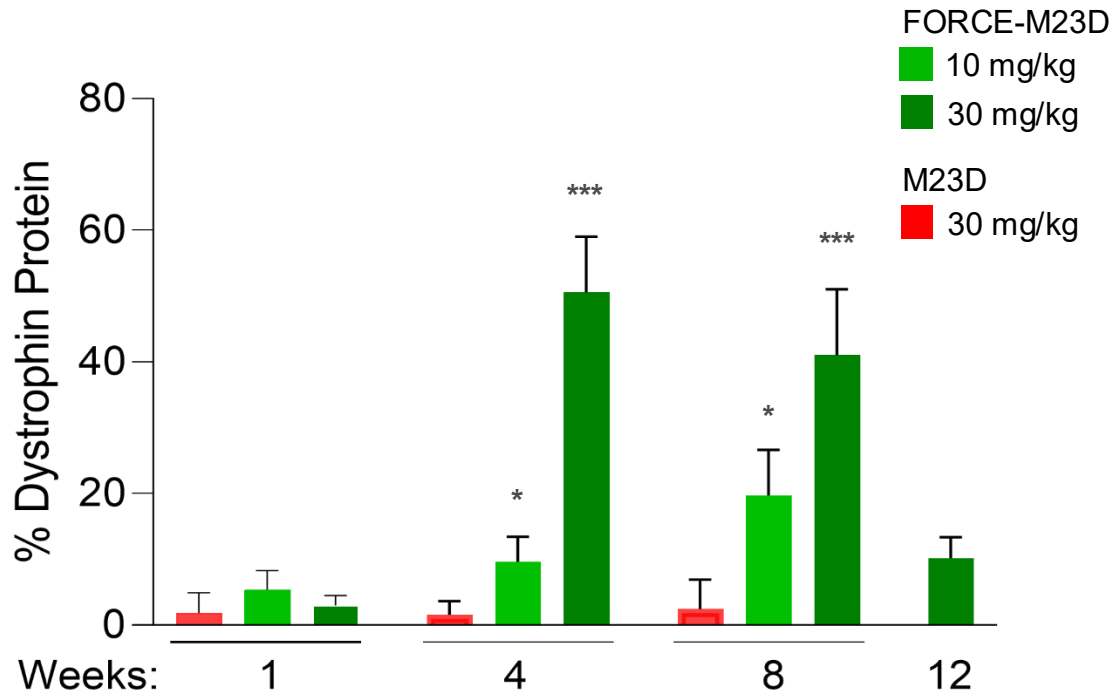
PCR, polymerase chain reaction; WB, western blot; IF, immunofluorescence

FORCE-M23D Achieved Robust and Durable Skipping and Expression of Dystrophin in Quadriceps

% Skipping by PCR



Dystrophin by WB



Note: Single IV dose of FORCE-M23D in *mdx* mouse model on day 0; Data are mean ±SD; N = 4 - 5 per cohort. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

Desjardins CA., et al. *Nucleic Acids Res*. 2022 Aug doi: 10.1093/nar/gkac641

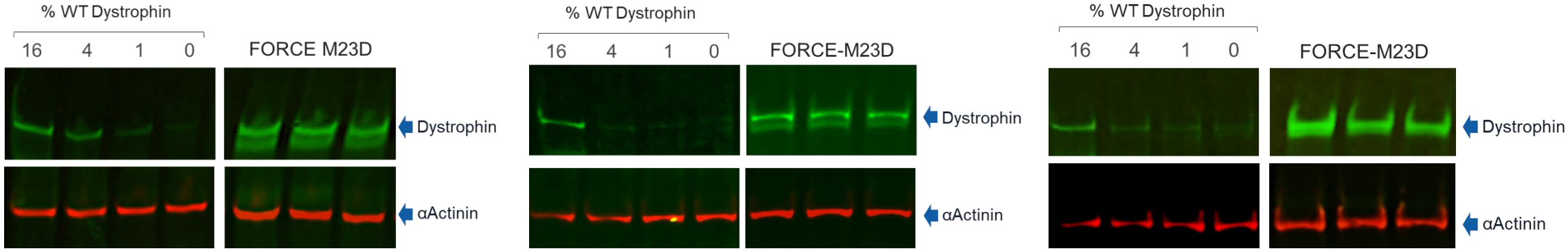
FORCE-M23D Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle

Quadriceps

Diaphragm

Heart

Dystrophin expression by WB

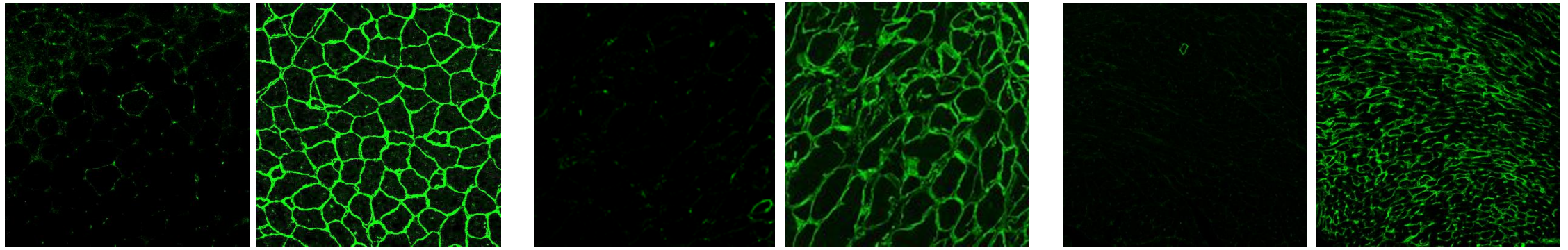


51% of wild-type dystrophin

90% of wild-type dystrophin

77% of wild-type dystrophin

Dystrophin localization to sarcolemma



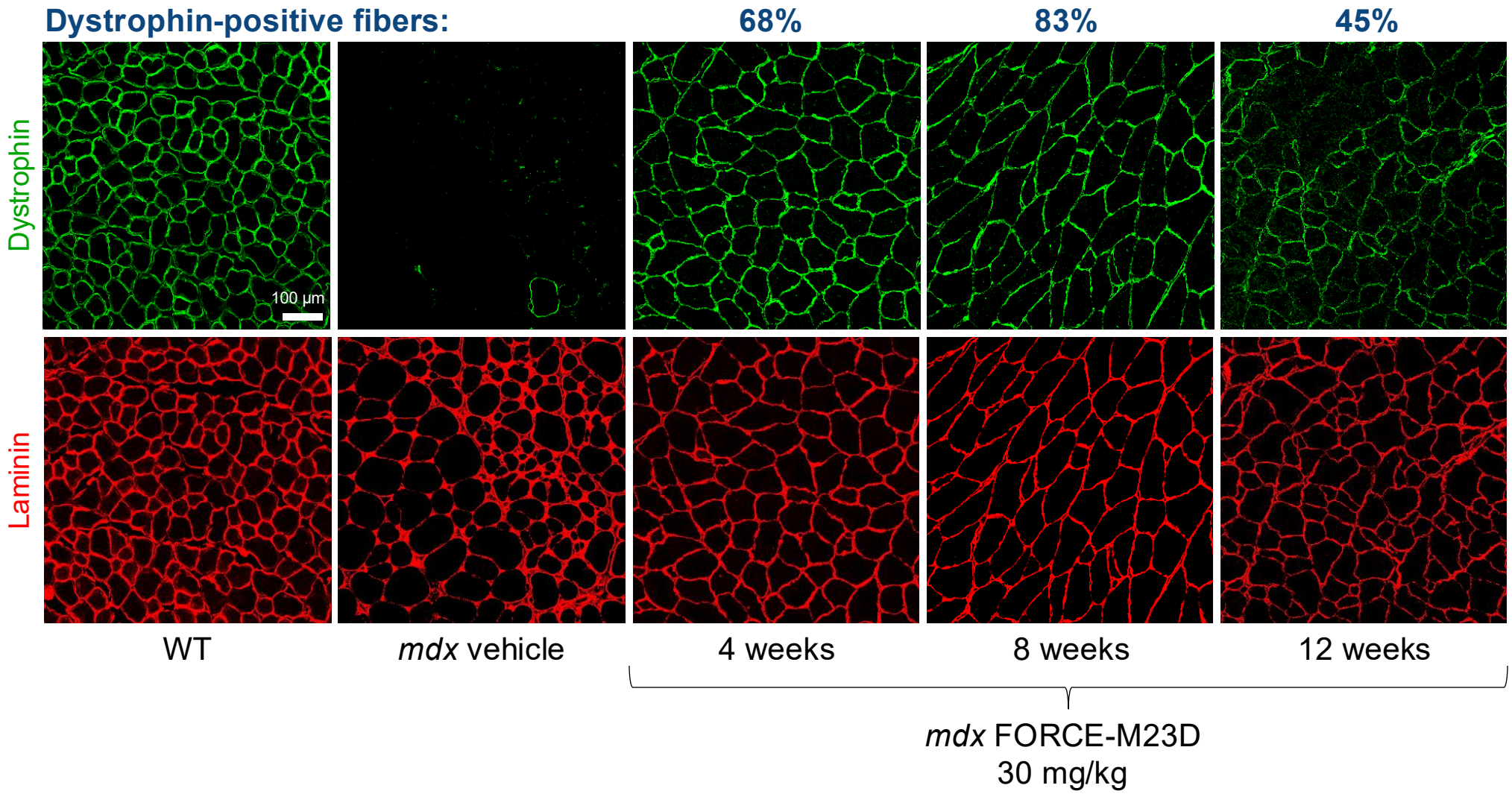
68% dystrophin-positive fibers

~80% dystrophin-positive fibers

~80% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; analysis on week 4 for all muscles. N= 3 - 5 per cohort

FORCE-M23D Achieved Durable Dystrophin Localization to Sarcolemma in Quadriceps



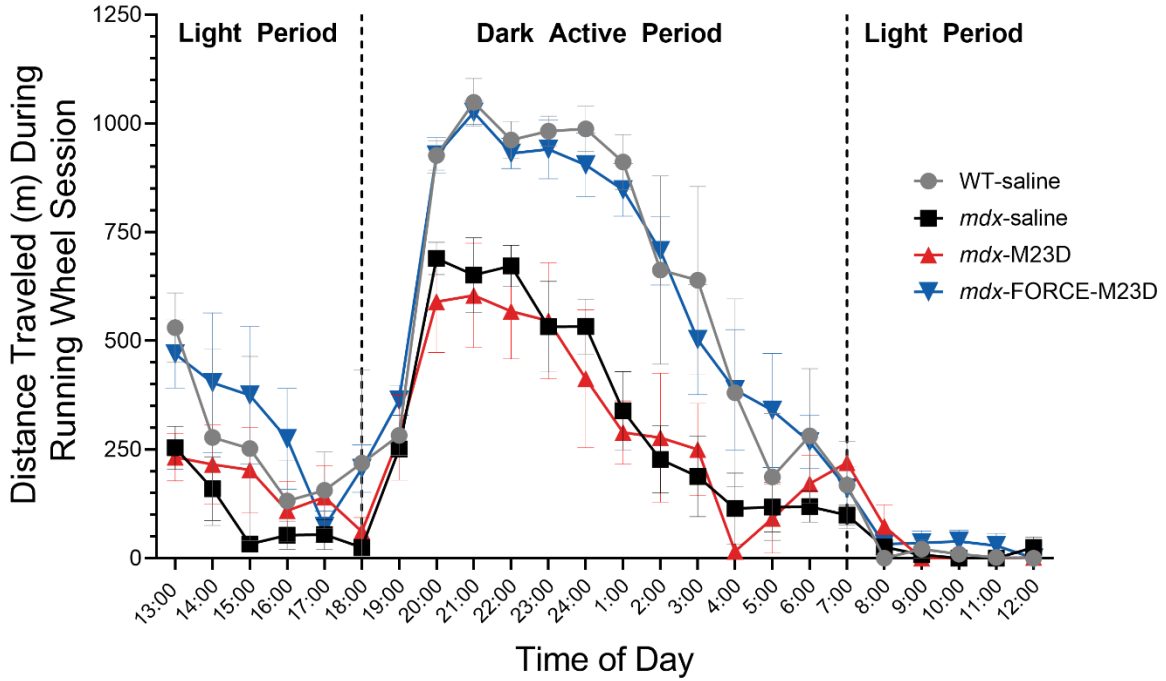
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis at specified time intervals

Desjardins CA., et al. *Nucleic Acids Res*. 2022 Aug doi: 10.1093/nar/gkac641

FORCE-M23D Demonstrated Functional Benefit with a Single Dose

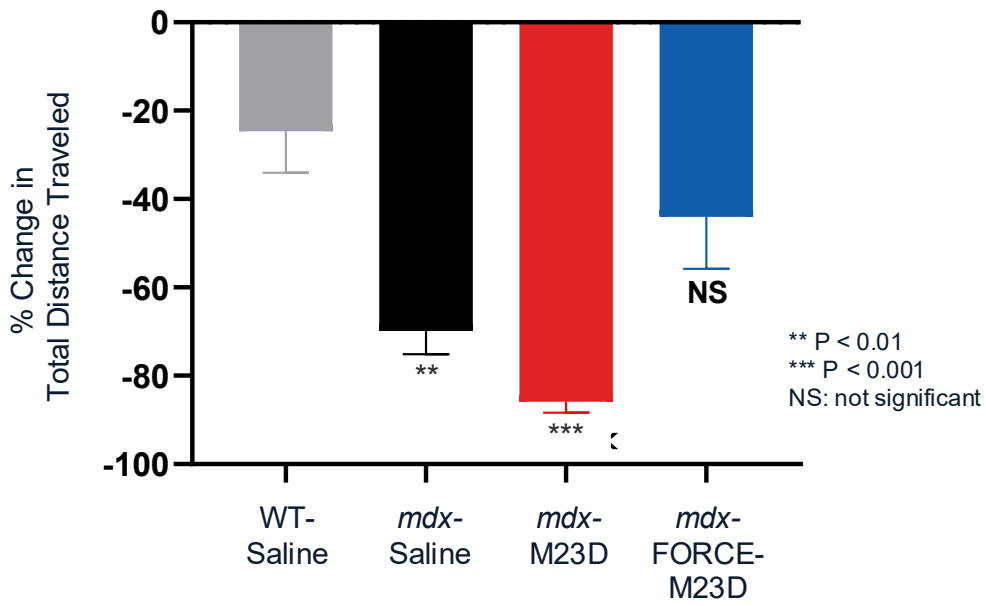
Distance Traveled in Home Cage Running Wheel

(Assessed 4 weeks after treatment)



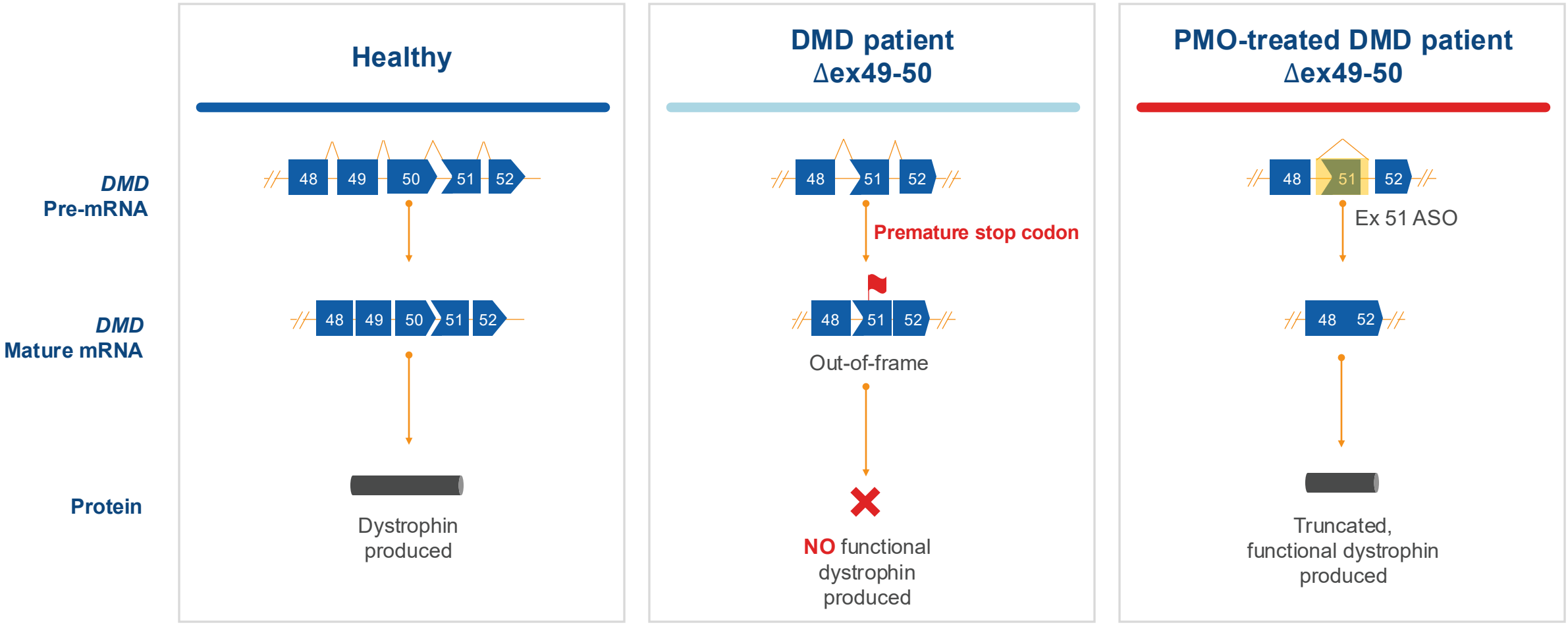
Distance Traveled in Open Field Following Hind Limb Fatigue Challenge

(Assessed 2 weeks after treatment)



Note: Single IV 30 mg/kg dose PMO in *mdx* mouse model. Hind limb fatigue challenge test statistical analysis comparison to WT group using one-way ANOVA with post-hoc Dunnett's test

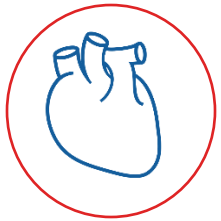
Targeting the Genetic Basis of DMD with a Proven Mechanism



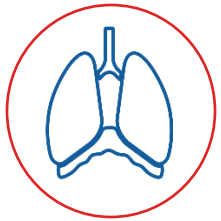
Adapted from Lim KRQ., et al. *Drug Des Devel Ther* 2017;11:533

DYNE-251 Demonstrated Robust Exon Skipping & Favorable Safety Profile in NHPs

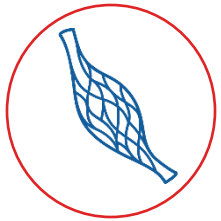
High Level of Exon 51 Skipping Achieved in Key Muscles at 2 Months[1]



43% in heart



52% in diaphragm



18% in quadriceps

GLP Toxicology Studies: 5-Week & 13-Week

- No dose limiting toxicity observed up to a maximally feasible dose
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested[2]

Notes: 1. Based on 5 weekly doses (Week 0 – Week 4) with tissue analysis at 8 weeks. 2. Based on conclusions of report from third-party CRO
NOAEL: No-observed-adverse-effect level

Phase 1/2 Clinical Trial to Evaluate DYNE-251 in Patients with DMD

Population

- Patients with DMD with mutations amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- ~46 male participants
- Ambulant and non-ambulant

Primary Endpoints

- Safety and tolerability
- Change from baseline in dystrophin protein levels by Western Blot

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Exon 51 skipping levels
  - Muscle tissue PDPF
  - Multiple assessments of muscle function, including NSAA score and certain timed functional tests

Stages of DELIVER

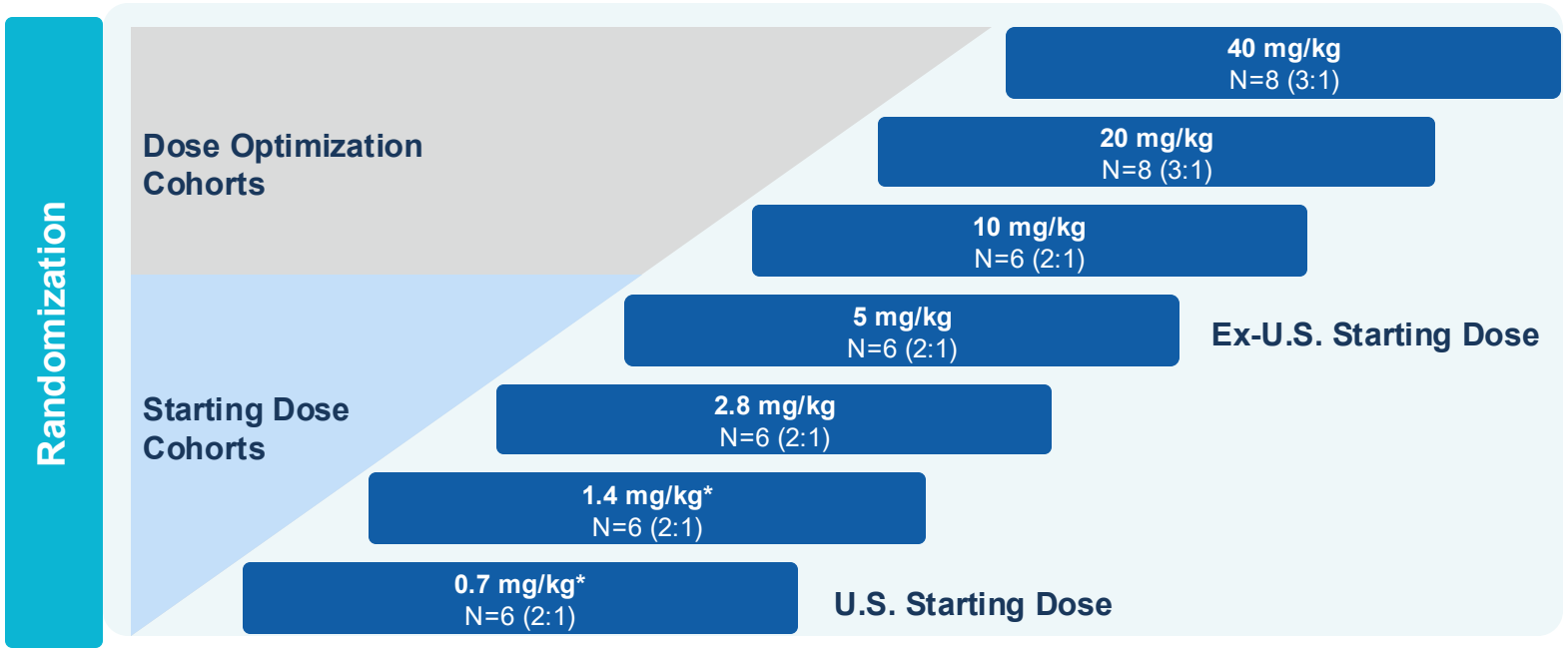
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Dystrophin Data Expected in H2 2023

Multiple Ascending Dose Stage of DELIVER

DELIVER

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly Administration of DYNE-251 in ~46 Ambulant and Non-Ambulant Male DMD Patients with Mutations Amenable to Exon 51 Skipping Therapy



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks
- Muscle biopsies: Baseline and 24 weeks in 2.8 mg/kg and higher cohorts
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Trial Designed to be Registrational and Enable Rapid Achievement of Predicted Pharmacologically Active Dose Levels

Dyne THERAPEUTICS

Patient cohorts will be dosed from 0.7 mg/kg to 40 mg/kg in the U.S. Outside the U.S., patient cohorts will be dosed from 5 mg/kg to 40 mg/kg. Doses provided refer to PMO component of DYNE-251.

* Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg and higher cohorts; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.

Driving Toward Meaningful Clinical Data in DM1 & DMD in H2 2023

ACHIEVE | DELIVER

Global, Randomized Placebo-Controlled Trials Designed to Be Registrational

Dosing Patients at Predicted Pharmacologically Active Doses

Significant Unmet Patient Need Provides Confidence in Ability to Enroll Rapidly

ACHIEVE	DELIVER
Safety, Tolerability & Splicing Data Expected in H2 2023	**Safety, Tolerability & Dystrophin Data Expected in H2 2023**

Dyne™ THERAPEUTICS

Targeting the genetic basis of serious muscle diseases to

STOP OR REVERSE DISEASE PROGRESSION

FORCE PLATFORM	**Robust** PIPELINE	**Delivering** FOR PATIENTS	**Exceptional** TEAM